Remodelling and restenosis: insights from animal studies

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Animal studies have been instrumental in elucidating the process of remodelling and its contribution to restenosis relative to neointimal formation following angioplasty. The majority of studies have utilized rabbit, porcine and nonhuman primate models of vascular injury. Despite the use of different experimental models, different forms of vascular injury, different methods of analysis and different definitions of arterial remodelling, all animal studies, with rare exceptions, have demonstrated the importance of remodelling in the maintenance of vascular patency in both atherogenesis and in restenosis following angioplasty. The finding that remodelling in the non-human primate is most comparable to that that occurs in man suggests that there may be a genetic predisposition to the balance of neointimal formation and arterial remodelling following vascular injury.

Key words: remodelling, animal models, vascular injury, restenosis

Introduction

Evaluation of remodelling of the arterial wall following acute injury in experimental models has taken on substantial importance because of an increasing awareness that intimal hyperplasia may not necessarily be the most important pathophysiological component of restenosis following angioplasty. Despite use of a variety of animal models and different experimental methods of vascular injury, these studies with rare exception have shown that remodelling of the arterial vessel wall following injury is crucial to the maintenance of vascular patency. This chapter will review some of the insights into remodelling and restenosis that have been gained from animal studies.

Rabbit models

Early studies utilizing morphometric analyses of the iliac arterial response to retrograde balloon pullback injury followed by cholesterol feeding in the New Zealand White rabbit concluded that progressive arterial luminal narrowing was due to the temporal increase in the size of the neointimal area [1]. These findings were consistent with the then contemporary belief that intimal

hyperplasia was the sole determinant of restenosis following balloon angioplasty. However, the study examined cross-sectional areas without preceding pressure fixation and the *in vivo* architecture of the vessel wall was not maintained at the time of analysis. Thus, any relationship between luminal narrowing, intimal and medial areas and the overall size of the artery could not be accurately ascertained. Moreover, ongoing studies in humans utilizing inhibitors of cellular proliferation in an effort to prevent the accumulation of neointimal cellular infiltrate were uniformly negative, suggesting that the pathophysiology of restenosis involved more than intimal hyperplasia alone [2]. These findings led to more detailed morphometric analyses in several different rabbit models of arterial injury. Preliminary studies demonstrated that intimal hyperplasia accounted for less than 50% of luminal narrowing in the non-atherosclerotic rabbit femoral artery 3 weeks following balloon dilation [3]. Thus, other processes must have contributed to the luminal renarrowing. Enlargement (remodelling) of the outer arterial circumference of uninjured, atherosclerotic aortae was shown to occur over 10 months in rabbits that were intermittently fed a 1% cholesterol diet [4]. Morphometric analyses 3–4 weeks following balloon angioplasty in rabbit femoral arteries which had lesions induced by air-drying and a 2% cholesterol-supplemented diet for four weeks revealed that the restenotic response was mediated by both chronic constriction (remodelling) and cellular proliferation [5]. Collectively, these studies led to the hypothesis that restenosis was only partly due to

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intimal hyperplasia and that remodelling of the injured arterial wall was an important component of the pathophysiology of arterial luminal renarrowing.

The importance of remodelling in restenosis was evaluated in detail by Kakuta et al. [6] who examined the morphometric changes in the atherosclerotic rabbit iliac model [7, 8] from immediately post angioplasty to 4 weeks following angioplasty when restenosis occurs in this model. The area circumscribed by the internal elastic lamina increased by 20% from acute to 4 week follow-up after angioplasty. Over the same time period, intimal area increased, but lumen area only slightly decreased because of the compensatory enlargement of the area circumscribed by the internal elastic lamina. The 4-week post-angioplasty group was divided into two subgroups: restenotic and non-restenotic. Surprisingly, the intimal areas of the two subgroups were virtually identical, despite, by definition, a smaller luminal area in the restenotic group. The difference in the lumen area between the groups was found to be the result of a significantly greater internal elastic lamina area in the non-restenotic group which had undergone compensatory enlargement. Although the internal elastic lamina and the intimal area correlatively increased in both groups, the slope of the correlation was less than one in the restenotic group and greater than one in the non-restenotic group, indicating that restenosis was due to less compensatory enlargement for similar increases in intimal area. The relation between intimal area and lumen area for all vessels in the chronic group demonstrated a biphasic relationship which showed that at small lumen areas, intimal area increased as lumen area decreased and at larger lumen areas, intimal area increased as lumen area increased. These authors concluded that arterial enlargement occurred after angioplasty in this atherosclerotic rabbit model and that differences in vascular remodelling initiated by balloon injury played a more important role than differences in neointimal formation in determining chronic lumen size. Thus, it is hypothesized that restenosis occurs in this model due to a failure of the artery to undergo adequate compensatory enlargement or 'favourable remodelling' in addition to neointimal formation. It is noteworthy that all the morphometric data in this study was measured directly without any geometric assumptions and that sampling of the arterial sections was done at 30 sites with an interval of less than 0.4 mm which allowed identification of the precise minimal lumen diameter. One important limiting consideration may be that the study utilized acute and chronic groups of different animals. It is conceivable that vessels in this model may compensatorily enlarge initially and then restenotic vessels undergo 'unfavourable remodelling' or constriction at some later time point within the 4-week post-angioplasty time period.

The potential for a combination of both lack of compensatory enlargement and a constrictive process has been suggested in a more recent landmark study by Lafont and coworkers [9]. In this study, focal femoral atherosclerosis was induced by endothelial desiccation

followed by 4 weeks of a 2% cholesterol diet at which time angioplasty was performed. The morphometry of the arteries was examined 3–4 weeks following angioplasty. Histological indices were defined as follows: (1) chronic constriction: the ratio of the area circumscribed by the external elastic lamina of the lesion site to that of a normal proximal reference segment; (2) neointimal-medial growth: difference between the area of the intima+media of the proximal reference site and the lesion site normalized by the intimal–medial area of the reference site; (3) adventitial growth: difference between the area of the proximal reference site and the lesion normalized by the adventitial area of the reference site; and (4) late residual restenosis: difference between lumen areas of the reference and lesion sites normalized by the lumen area of the reference site. Another parameter defined as the ratio of the adventitial area to the area of the intima+media at the lesion site allowed evaluation of the relative importance of these layers. Surprisingly, late residual restenosis correlated with chronic constriction, but not neointimal-medial or adventitial growth, suggesting that restenosis was independent of the degree of neointimal growth, which agrees with the hypothesis of Kakuta et al. [6]. In contrast to the latter study, the degree of constriction among the lesions was observed by Lafont et al. [9] to be more of a continuum than a bimodal distribution with some arteries exhibiting constriction and others exhibiting compensatory enlargement (constriction indices of <1 and >1, respectively). The data indicated that there was not only a lack of compensatory enlargement, but also a constrictive component that influenced the outcome, since restenotic arteries were identified with increased intimal–medial growth without compensatory enlargement or constriction, arteries that exhibited generalized constriction without marked increases in neointimal–medial growth, and arteries with a mixed response with varying degrees of neointimal–medial growth and either constriction or enlargement. These data are in agreement with the complex and diverse pathophysiologies involved in restenosis. This model also showed a strong inverse correlation between neointimal–medial growth and chronic constriction. This finding suggests that either a lack of neointimal growth results from chronic constriction or that compensatory enlargement follows neointimal growth. The latter possibility was observed by Kakuta et al. [6] since varying degrees of compensatory enlargement were observed for different amounts of intimal–medial growth. However, some robust intimal hyperplasia occurred in this model and the differences in the remodelling process may reflect different responses to vascular injury. On the other hand, differences in analytical methodologies may also contribute to discrepant findings since the previous study did not normalize data to a proximal reference segment, whereas Lafont et al. [9] did so in order to minimize animal-to-animal variations. In this latter study, there was no correlation between adventitial growth alone with constriction; however, the ratio of the adventitial

to intimal–medial areas at the lesion site correlated with chronic constriction, suggesting that constriction may be influenced by altered balance between the relative size of the intimal–medial and adventitial areas in favour of the adventitia. These authors suggest that the relative dominance of the adventitia may impair compensatory enlargement and result in an apparent chronic constriction. However, it is important to note that since a strong inverse correlation was observed between neointimal–medial growth and chronic constriction, and, there was no correlation between adventitial growth and chronic constriction, the possibility exists that if the normalized adventitial growth was similar among all vessels then the ratio of adventitial growth to neointimal–medial growth mathematically would be expected to correlate with chronic constriction. Thus, it is possible that the adventitia may not play as dominant a role in arterial remodelling in this rabbit model as proposed. Studies in other animal models to be discussed below have addressed the role of the adventitia more directly.

Several studies have examined the relative contribution of neointimal formation and remodelling to restenosis in different rabbit models using different methods of morphometric analyses which have shown contrasting results [10, 11]. Post et al. [10] examined intimal hyperplasia and remodelling in normal rabbit femoral arteries that were pressure perfusion fixed 3 and 8 weeks after conventional or thermal (37°C or 55–90°C) angioplasty. In this model the neointima was defined as any tissue circumscribed by the internal elastic lamina. The potential cross-sectional lumen area was calculated from the perimeter measurement of the internal elastic lamina, assuming a perfect circular configuration. This calculated measurement was then presumed to be representative of the luminal area which would have been observed if there was no neointimal hyperplasia following vascular injury. The actual lumen area reported in this study was calculated by subtracting the area of the neointima from the calculated potential lumen area and then this area was assumed to be a perfect circular area. The difference between the radius of potential and actual lumen, as derived from their respective cross-sectional areas, was taken as the average thickness of neointima which, by virtue of these calculations, was assumed to be a perfect annular configuration. To assess the contribution of intimal hyperplasia, the doubled mean intimal thickness (that portion of the lumen diameter accounted for by neointimal formation) was then compared to angiographic late loss or restenosis which was defined as the difference in angiographic diameter at the time of euthanasia and post-dilation diameter. The difference in late loss and doubled mean intimal thickness showed a discrepancy in which intimal hyperplasia could only account for 14–23% of late loss (doubled mean intimal thickness divided by late loss). This unexplained discrepancy in the reduction of luminal diameter versus intimal hyperplasia was defined as remodelling and was reported to be the major determinant of restenosis in

this model. Similar findings were observed in normal and atherosclerotic Yucatan pig models to be discussed below. Intuitively, the validity of the geometric assumption of annular neointimal formation is difficult to assess since in most human and in some animal models restenosis develops eccentrically as it did to some extent in this study. Although some of the pitfalls in the comparison of angiographical and histological dimension are mentioned, it also should be noted that single plane angiography can lead to very erroneous results due to eccentricity of the stenoses. In a worst case scenario, the formation of completely eccentric neointima occluding 50% of the restenotic artery in the form of a 'half-moon' could be observed as a 50% occlusion in one plane and would be perceived as normal when viewed at 90° to that plane. Thus, caution should be used in interpreting calculations based on circular geometry. However, it should be noted that Post et al. [10] have utilized this analysis in a model which is more appropriate to the assumptions of annular neointimal formation and the data do reflect a difference in the relative contribution of neointimal formation and remodelling. In contrast to these studies, other studies utilizing a rabbit model have found that remodelling is not the principal pathogenic process in restenosis [11]. Gertz et al. [11] analysed pressure perfusion fixed segments of rabbit femoral arteries 2 hours and 28 days following four subcategories of interventions at 1 month post induction of focal atherosclerosis by endothelial desiccation and atherogenic diet. In this study, arterial size and the reference or largest luminal area was calculated assuming a perfect circle using the perimeter measurement of the external elastic lamina and the perimeter measurement of the lumen, respectively. However, these authors measured the minimal luminal area directly in contrast to calculation from the perimeter [10] which would inappropriately normalize luminal irregularities likely to be present in vivo. The cross-sectional area narrowed by neointima, expressed as a percentage, was calculated as the (area circumscribed by the internal elastic lamina minus the luminal area) × 100 divided by the area circumscribed by the internal elastic lamina. The four interventional strategies employed were: (1) balloon angioplasty; (2) balloon angioplasty followed by treatment with antistatin (factor Xa inhibitor); (3) combined balloon angioplasty and laser; or (4) no angioplasty. The results demonstrated an initial post-interventional gain in luminal diameter at the sites of angioplasty followed by a significant reduction in angiographic diameter and histomorphometric luminal cross-sectional area 28 days post-procedure compared to adjacent non-angioplastied segments of the same arteries, to non-angioplastied control arteries, or to angioplastied segments of animals treated with antistatin. By contrast, the overall size of the arteries at the sites of restenosis was not significantly different from the majority of adjacent non-angioplastied arteries, and the mean arterial size at the sites of restenosis was not significantly different from corresponding segments of non-angioplasty control

segments or from angioplastied segments of animals treated with antistatin. In the minority of angioplastied arteries in which the arterial size did change, the arteries enlarged. These authors concluded that luminal cross-sectional narrowing by plaque and not geometric remodelling (defined as a decrease in arterial size) was the principal morphological feature associated with restenosis after angioplasty in this model. The numerical data invites re-interpretation, as does the finding that the segment most narrowed by plaque was not always the segment identified as the smallest luminal area which directly states that the process of restenosis involves more than neointimal formation if the geometric assumptions in the methodology are valid. Perhaps the most obvious limitation to the study is that non-restenotic vessels were not subcategorized. It is possible that the restenosis reported in this study was due to neointimal formation and a failure to compensatorily enlarge if there was a relationship between non-restenotic arteries and arterial size as reported by Kakuta et al. [6]. In this case, it could not be concluded that arterial remodelling did not play a significant role in this restenotic model. This latter point illustrates the need for standard animal models, analytical methods and definitions of remodelling, all of which can affect conclusions on the relative contribution of remodelling and neointimal hyperplasia in restenosis.

Porcine models

Injury of porcine coronary arteries either by angioplasty using an oversize balloon or placement of an over-expanded stent or tantalum wire coil stimulates the formation of vascular lesions morphologically similar to those seen in human post-angioplasty restenosis [12, 13]. Recently, remodelling has been investigated by several different laboratories using the porcine model. Andersen et al. [14] reported that remodelling rather than neointimal hyperplasia was responsible for luminal narrowing after deep coronary vessel wall injury. In this study, coronary injury was induced using a "chain-encircled" balloon sized so that the ratio of the balloon and encirculating chain to the artery was approximately 1.6:1. The chain-encircled balloon was inflated in the left anterior descending coronary artery and then pulled back to create a deep circumferential injury that removed the tunica media out to the adventitia. Animals in two groups were followed by either serial angiography at pre-, 2 hours, 2 and 4 weeks post dilation or sacrificed at 3 weeks post dilation when the neointimal healing response is at a maximum [15]. Serial in vivo angiography in group I revealed a late loss in lumen diameter that was identical to that observed in group II using a post-mortem angiographic technique to visualize the pressure perfusion fixed coronaries in situ. Histology revealed a neointimal area at the site of maximal narrowing which equated to a neointimal thickness, assuming a perfect annular configuration, that

could only account for no more than 30% of the late luminal loss. These authors concluded that constrictive vascular remodelling was responsible for at least 70% of the late loss in this (re)stenosis model. These findings are similar to those found in the normal and atherosclerotic Yucatan micropig iliac balloon denudation model which showed that the percentage of late loss explained by neointimal hyperplasia was only 11% in the normal group and 49% in the atherosclerotic group [10]. Both studies used the geometric assumption that neointimal formation occurred in a perfect annular configuration. The pitfalls of this assumption have been discussed in detail previously. However, these studies provide evidence that the process of (re)stenosis in the porcine model likely involves both neointimal formation and remodelling.

The concept that remodelling is a constrictive process in the porcine model is supported by several other recent studies which have focused on the contribution of adventitial changes following vascular injury [16, 17] Shi and coworkers [16] examined cellular content and composition, extracellular matrix deposition and thickening in the adventitia three, seven, 14 and 28 days following oversize coronary balloon inflation injury in the normocholesterolemic pig. The cell density increased by the third day and returned to baseline by 14 days post injury. The increase in cell density was paralleled by high proliferative activity in the adventitia. Coronary injury caused α-smooth muscle actin and desmin expression to increase above controls at 7 and 14 days, indicating the presence of adventitial myofibroblasts which may have arisen from phenotypically transformed fibroblasts which invaded the area of injury. The above changes leading to myofibroblast formation were associated with a striking accumulation of collagen-containing scar tissue in a greatly thickened adventitia which was thicker than controls at all time points. The accumulation of contractile cytoskeletal proteins in myofibroblasts, in particular α-smooth muscle actin, has been a hallmark of collagen matrix remodelling in vitro and in vivo [18, 19]. In the presence of increased collagen deposition, adventitial myofibroblasts may contribute to the process of scar contracture during wound healing [19] and it is postulated by Shi et al. [16] to represent a putative mechanism of vessel constriction that has recently been reported to correlate with restenosis following angioplasty [9]. On the other hand, the presence of increased adventitial collagen may contribute to a stiff, 'collar-like' adventitia that prevents coronary dilation during neointimal formation. Thus, the adventitial changes following coronary injury may cause unfavourable remodelling or prevent compensatory enlargement. Scott et al. [17] suggested similar conclusions using a balloon overstretch porcine model. In addition, these authors hypothesized that the adventitia could also contribute to lesion formation by contributing to the cellular mass of the neointima via migration into the neointima by replicating cells of adventitial origin. Hence, studies in porcine models have suggested that both unfavourable remodelling and

Table 1. Animal models and arterial remodelling

Animal	Diet	Primary injury	Observed arterial remodelling
Rabbit (5, 9)	Atherogenic	Endothelial desiccation	Chronic constriction, compensatory enlargement, lack of compensatory enlargement
Rabbit (6)	Atherogenic	Balloon de-endothelialization	Compensatory enlargement
Rabbit (3, 10)	Normal	Conventional thermal angioplasty	Chronic constriction
Rabbit (11)	Atherogenic	Endothelial desiccation	None or slight compensatory enlargement with luminal narrowing due to neointimal formation
Rabbit (4)	Atherogenic	None	Compensatory enlargement
Swine (14)	Normal	Chain encircled balloon pullback	Constriction
Yucatan pig (10)	± Atherogenic	Balloon de-endothelialization	Constriction
Swine (16, 17)	Normal	Oversize balloon dilation	(Adventitial) constriction
Primate (20, 22)	Atherogenic	None	Compensatory enlargement
Primate (21)	Atherogenic	Conventional angioplasty	Compensatory enlargement with plaque fracture, delayed recoil and intimal hyperplasia as in man

neointimal formation explain luminal narrowing and that vascular constriction may be due to adventitial changes following injury.

Primate models

There is a paucity of data from studies utilizing non-human primate models which is most likely due to the expense of the model. However, the few studies which have compared man with the atherosclerotic non-human primate [20] and the restenotic non-human primate [21] have shown that arterial remodelling is remarkably similar among primates. In contrast, other animal models are not nearly as comparable to man. These studies suggest that the balance between neointimal growth and arterial remodelling may be tipped in either direction by inherent genetic characteristics. In primate atherosclerosis, on average, lumen size is unaffected by plaque size [20]. Although the ratio of the intima to lumen increases, the absolute lumen size does not as a rule decrease in experimental primate atherosclerosis [22]. The maintenance of lumen size is possible because both the media and intima yield to hydraulic forces to compensatorily enlarge in an outward direction [22] and there is a trend to···ard overcompensation [20]. This also suggests that a thickened adventitia does not have a rigid inner boundary, despite considerable fibrosis, as has been suggested for porcine models [16]. The similarity of remodelling in human and non-human atherosclerotic primates suggests that the process has general biological significance. The lack of compensatory enlargement may be a major determinant of whether a person with coronary artery disease develops its complications. Similarly, the response to angioplasty in non-human primates appears to closely resemble that in humans [21]. Plaque fracture, delayed recoil, intimal hyperplasia and remodelling may be important in determining late lumen calibre. Thus, these non-human primate models that more closely mimic the response to injury of atherosclerotic human arteries may prove invaluable in defining the role of remodelling in atherosclerosis and restenosis, thereby elucidating clinically useful therapeutic targets in man.

Summary (Table 1)

Rabbit studies have suggested that remodelling following arterial injury occurs as a result of lack of compensatory enlargement, constriction of overall vessel size as well as a mixed response dependent upon the degree of neointimal formation with either enlargement or constriction. Remodelling in the porcine models has largely been reported as a constrictive process that is relatively more important than neointimal formation and may involve changes in the adventitia following vascular injury. In contrast, non-human primate models have reported that remodelling is a compensatory enlargement process which most closely resembles that which occurs in man. The latter studies suggest that it is the lack of compensatory enlargement that is responsible for the clinical manifestation of atherosclerosis and restenosis in man. The various conclusions using different models of the same species, different species, different analytical methods, and different definitions of remodelling generally agree that remodelling is a more important component than neointimal formation in the maintenance of vascular patency following injury, however, the mechanistic processes remain to be elucidated and may depend, in part, on study methodologies. The most promising model for studying the remodelling process which may mimic that found in man, may be the non-human primate.

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